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From: Karen R. Zachow, Ph.D. **Date:** September 3, 2003

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Comments:

ATTORNEY DOCKET:	377882001300
GROUP ART UNIT:	1636
EXAMINER:	D. Sullivan
SERIAL NO.:	09/802,445
FILING DATE:	March 9, 2001
INVENTOR(S):	Gary VAN NEST and Joseph J. EIDEN, Jr.
TITLE:	METHODS OF REDUCING PAPILLOMAVIRUS INFECTION USING IMMUNOMODULATORY POLYNUCLEOTIDE SEQUENCES

Papers attached:

1. Transmittal Form (1 page)
2. Declaration of Gary Van Nest (5 pages)

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PTO/SB/21 (05-03)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/802,445
Filing Date	March 9, 2001
First Named Inventor	Gary VAN NEST
Art Unit	1636
Examiner Name	D. Sullivan
Total Number of Pages in This Submission: 6	Attorney Docket Number: 377882001300

ENCLOSURES (*check all that apply*)

- [ ] Fee Transmittal Form
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- [ ] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
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- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
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- [ ] CD, Number of CD(s) ____
- [ ] After Allowance Communication to Group
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- [ ] Proprietary Information
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- [x] Other Enclosure(s) (please identify below):

Declaration of Gary Van Nest (5 pages)

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Signature	Karen Zachow
Date	September 3, 2003

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Docket No.: 377882001300
(PATENT)

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In re Patent Application of:
Gary VAN NEST and Joseph J. EIDEN, Jr.

Application No.: 09/802,445 Group Art Unit: 1636

Filed: March 9, 2001 Examiner: D. Sullivan

For: METHODS OF REDUCING PAPILLOMAVIRUS INFECTION USING IMMUNOMODULATORY POLYNUCLEOTIDE SEQUENCES

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DECLARATION OF GARY VAN NEST, PH.D.
PURSUANT TO 37 CFR §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Gary VAN NEST, Ph.D., hereby declare as follows:

1. I currently reside at 639 Skyline Drive, Martinez, California 94553.

2. I am an inventor named in the above-referenced patent application, and am familiar with the written communication from the Patent Office dated March 7, 2003.

3. Described herein are results from additional experiments performed in a similar manner to the experiments described in Example 2 in the patent specification. I participated in the design of these additional experiments. The results from these experiments demonstrate that ISS treatment induces regression of a papilloma lesion whether the ISS is administered at the site of the lesion (locally) or at a site distant from the lesion (systemically).

4. As described in Example 2 on page 45 of the specification, cottontail rabbit papillomavirus genomic DNA CRPV-mE8 induces small, slow growing papillomas when inoculated

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in rabbit skin. Prior to DNA inoculation, the skin was made hyperplastic using a mixture of turpentine and acetone.

5. Rabbits were inoculated with 10 μg of CRPV-mE8 DNA, at a total of six different sites per animal, three sites on the left side of the back and three sites on the right side of the back. The sites were monitored for papilloma growth until sufficient papilloma sites were available for treatment. Using this procedure, typically 60% of the inoculated sites produce papillomas. As expected, in this case, examination of the individual rabbit papilloma growth showed that a number of viral DNA inoculation sites failed to generate papillomas. To prevent the possibility of treating sites that failed to produce a papilloma, treatments were delayed until sufficient sites showed growing papillomas (56 days after viral DNA inoculation).

6. The rabbits were divided into five treatment groups, each consisting of 4 rabbits. Each rabbit received either ISS oligonucleotide (5'-TGACTGTGAACGTTCGAGATGA-3' (SEQ ID NO:1) or PBS, as follows:

Group	Treatment	Number of sites treated
A	500 μg ISS 1 X/week for 6 weeks	10
B	500 μg ISS 3 X/week for 6 weeks	10
C	1000 μg ISS 1 X/week for 6 weeks	10
D	PBS 1 X/week for 6 weeks	9
E	PBS 3 X/week for 6 weeks	9

7. One of the rabbits that contributed three treated papilloma sites for each of the phosphate-buffered saline (PBS) control groups showed systemic regression of all sites prior to treatment and was removed from the study. Therefore, the PBS control groups had only 6 treated papilloma lesion sites for evaluation.

8. In all rabbits, the left side papillomas were treated with ISS or PBS, the right side papillomas were left untreated. All treatments were delivered intralesionally into the base of the papilloma.

9. During the study, the size of the papillomas were measured weekly in three dimensions and a geometric mean diameter was calculated. When the growth rates of the ISS-treated versus PBS-treated papillomas were compared for each group, Groups A, B, and C (ISS-treated groups) showed significant growth reductions compared to the PBS-treated control group

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papillomas, as herein presented in Exhibit A. The growth curves for the Group A and Group C papillomas versus Group D and for Group B versus group E are shown in Exhibit A. In groups A and C, a nearly complete inhibition of papilloma growth can be noted immediately after the start of ISS treatment.

10. In addition to inhibition of papilloma growth, ISS treatment induced regression of some papillomas as shown in Table 1. Notably, 4 out of 10 treated sites regressed in Group C, animals that received 1000 μg ISS once per week.

Table 1. Papilloma regression induced by ISS treatment.

Group	Sites Treated	Sites Regressed
A	10	2
B	10	1
C	10	4
D	6	1
E	6	0

11. Since each treated rabbit also had untreated papilloma sites on the right side of the back, this experiment enabled assessment of the effect of ISS treatment on regression of papillomas at sites distant from ISS treatment (i.e., systemically treated lesions). This data is presented in Table 2.

Table 2. ISS treatment induces papilloma regression at local and distant sites.

Group	Sites and their Treatment	Regressions/sites
Group A (ISS)	Left side, locally treated	2/10
	Right side, distantly treated	2/7
	Total	4/17 (24%)
Group B (ISS)	Left side, locally treated	1/10
	Right side, distantly treated	0/4
	Total	1/14 (7%)
Group C (ISS)	Left side, locally treated	4/10
	Right side, distantly treated	3/7
	Total	7/17 (41%)
Group D (PBS)	Left side, locally treated	1/6
	Right side, distantly treated	data not available
	Total	data not available
Group E (PBS)	Left side, locally treated	0/6
	Right side, distantly treated	1/6
	Total	1/12 (8%)

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12. As demonstrated in Table 2, the groups treated weekly with ISS (Groups A and C) showed regression of both locally treated papillomas and systemically treated, distant papillomas. In Groups A and C, the percentage of papillomas showing regression was similar or higher for systemically treated, distant sites compared to locally treated sites. Comparisons of papilloma regression in Group E to that of Group A or C show that animals treated with PBS alone did not show this percentage of papilloma regression, *i.e.*, 8% compared to 24% or 41% regression. These data indicate that ISS treatment has a systemic effect and can induce papilloma regression at sites distant from ISS delivery.

13. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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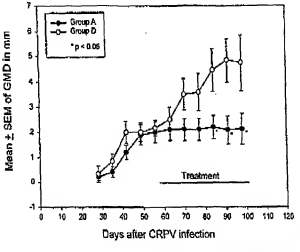
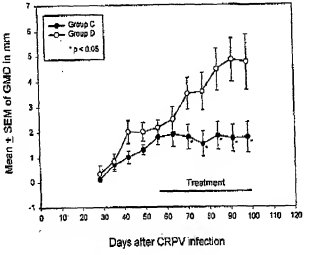
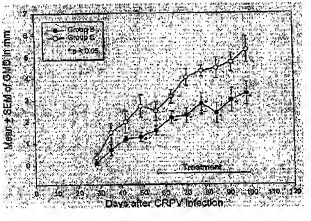
Application No.: 09/802,445 Docket No.: 377882001300

Exhibit A.

Effect of ISS treatment on rabbit papillomas







* p<0.05 compared to control, PBS treated group

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